REMARKS

Reconsideration is requested.

Page 1 of Paper No. 11 (Office Action dated August 8, 2002) indicates the drawings have been objected-to however the undersigned has not received a PTO-948 Form, nor has the Examiner indicated the same has been mailed, indicating any specific objections to the drawings. Paper No. 11 does not elaborate any specific objection to the drawings. The Examiner is requested to provide an indication of any specific objection of the drawings, to which the applicants will reply with corrected/formal drawings. The applicants note that drawings were not believed to have been filed September 7, 2000, as indicated by the Examiner on page 1 of Paper No. 11.

The claims have been amended to advance prosecution, without prejudice, and to place the application in condition for allowance

The claims have been amended with the Examiner's comments in mind. The amendments are not believed to raise new issues requiring further search and/or consideration and entry of the amendments is requested, with allowance of the claims.

The Section 102 rejection of claims 1, 2, 4 and 6 and the Section 103 rejection of claims 3 and 7-10, over Meucci (U.S. Patent No. 5,135,875) are moot in view of the above. The newly added claims are submitted to be patentable over Meucci, which teaches an immunoassay which requires multiple steps to recover the indicated analyte. The presently claimed invention is submitted to be patentable over Meucci. The Examiner is requested to consider the following in this regard.

According to Meucci (for example, claim 11) a precipitation reagent is used to remove the interfering proteins from a biological test sample prior to the immunological detection of the hydrophobic analyte in the resulting extract.

As indicated in col. 3, lines 25 – 52 of Meucci, preferably, the treated sample, with the precipitation reagent, is centrifuged to remove the interfering proteins, resulting a supernatant containing the hydrophobic analyte. The first step of the immunological detection of the analyte is to combine such supernatant with a detectable tracer compound and an appropriate antibody to, or binding agent for, the analyte, prepared according to methods known in the art.

The precipitation reagent in Meucci (col. 1 lines 50 – 65 and col. 2 lines 25 – 39) precipitates the interfering proteins from a biological test sample, while, at the same time, maintaining hydrophobic analytes in solution and minimizing the denaturation of specific binding proteins, such as, for example, antibodies, which may be present in an immunoassay system.

The denaturation of specific binding proteins, such as antibodies is minimized in Meucci, by inclusion of the glycol component of the precipitation reagent (col. 2, lines 55 - 64). Specifically, Meucci teaches that glycol decreases the toxicity of the other components, particularly the alcohol component, and stabilizes cellular receptors and specific binding proteins which are employed in an assay system, particularly antibodies, by preserving the binding integrity thereof.

The precipitation reagent in Meucci therefore is adapted to the immunoassay conditions described therein.

The precipitation reagent in Meucci is employed to extract hydrophobic analytes from proteins present in the test sample, wherein proteins are precipitated while, at the same time, recovering from between about "90% and 110%" of the extracted analyte (col. 3, lines 15 to 22).

Meucci uses an immunoassay, particularly a fluorescence polarization immunoassay. It demands many steps, including the preparation of specific reagents such as the tracer compound and an appropriate antibody as described by Meucci et al (col. 4 lines 51-68, col. 5 lines 1-24 and the example at col. 5 lines 28-68, col. 6 lines 1-68, col. 7 lines 1-43). The method of Meucci provides high sensitivity – 15.0 nanograms/ milliliter of cyclosporine and metabolites (col. 7 lines 18-20).

Accordingly, Meucci teaches the use of a specific precipitation reagent which extracts the drug from the body fluids to be detected by a complex method of high sensitivity.

Contrary to Meucci, the method of the present invention provides the following:

a) detection of drugs, in general, in a test sample, which are not limited to only hydrophobic analytes, as in Meucci, measured by an immunoassay system to detect the drug level (claim 8, Summary of the invention); and

b) a simplified and effective deproteinizing step from body fluids, such as plasma, blood, urine, saliva, tear fluid, in an accurate technique, such as a colorimetric assay or a High-Performance Liquid Chromatography method, to detect the drug concentration.

Consequently, the presently claimed invention does not require addition of "a detectable tracer compound and an appropriate antibody to, or binding agent for, the analyte, prepared according to methods known in the art", or a glycol component as a

precipitation reagent, such as is required of Meucci; or a precipitation reagent of Meucci as further shown in the following table:

Meucci et al	Present Invention
about 5.0 mM to about 100.00mM of a Zinc salt (sulfate, chloride and acetate) participates in the precipitation of interfering proteins	Zinc sulfate (0.1M to 5.0 M)
between about 5% (w/v) and about 50% (w/v) of a glycol, a glycerol or a combination thereof	
About 30% (w/v) to about 100% (w/v) of a straight or branched chain alcohol having from 1 to 4 carbon atoms, selected from methanol, ethanol, propanol, butanol and mixtures thereof (The alcohol component "participates in maintaining the hydrophobic analyte in solution, and precipitates proteins and conjugated proteins" (col.2 lines 51– 54).	An appropriate solvent polar - H_2O, alcohols and mixtures; nonpolar – acetonitrile/2-propanol, benzene, toluene, dichloromethane, chloroform or its mixtures. (depending on the solubility properties of the drug which is being measured), used to extract the drug
About 0%(w/v) to about 20% (w/v) of An acid component, selected from, 5-sulfosalicylic acid, trichloroacetic acid, hydrochloric acid, acetic acid and the like (to precipitate and denature interfering proteins (col. 2, lines 67-68)).	an antioxidizing (optionally) ascorbic acid (to slow down the occurrence of oxidation reaction)

The presently claimed invention involves a deproteinizing step in the presence of zinc sulfate to efficiently strip off the drug, which became bound to proteins contained in biological fluid, using an appropriate solvent [polar (H_2O, alcohols and mixtures), non polar or mixtures thereof], depending on the solubility properties of the drug.

In the teaching of Meucci, not only does the zinc sulfate participate in the deproteinizing step, but also the alcohol component and, eventually, an acid component The alcohol component also maintains the analyte in solution.

The glycol component, which is indispensable to Meucci, is not required in the present invention.

The acid components in the present invention, particularly ascorbic acid, does not precipitate and denature proteins, as used in Meucci. Rather, the acid components of the presently claimed invention and antioxidants, slowing the occurrence of oxidation reaction.

The applicants believe the above-noted differences demonstrate that the presently claimed invention is not described in Meucci et al. and the Section 102 rejection of claims 1, 2, 4, and 6 over Meucci should be withdrawn.

The above-noted differences between Meucci and the presently claimed invention provide important differences for the drug detection method of the present invention as compared with the cited art. The claimed invention allows drug detection in body fluids down to at least 0.3 µg/ml, using detection methods, such as colorimetric assays (FIGURES 4A and 4B), that are simpler and faster than immunoassays. The stronger concentration of zinc sulfate in a smaller added volume and the appropriate solvent to extract the drug (Example 1) made possible the recovery of at least 97% of the drug through a simplified and effective deproteinizing step from body fluids.

The claims are submitted to be patentable over Meucci.

The Section 103 rejection of claims 5 and 11-21 over Meucci in view of Lam (J. Liquid Chromatography, 12(10), 1851-1872 (1989)) will be moot upon entry of the

above amendments. The above claims are submitted to be patentable over Meucci in view of Lam and consideration of the following in this regard is requested.

The solvent of the presently claimed invention extracts the drug during the deproteinizing step which is not provided for or suggested by the cited art.

In Meucci et al the glycol component is necessary in the immunoassays of Meucci to decrease the toxicity of the other components, particularly the alcohol component, and to stabilize cellular receptors and specific binding proteins which are employed in an assay system of Meucci, particularly antibodies, by preserving the binding integrity thereof.

Both Lam, and Bergqvist, teach precipitation with zinc sulfate in an appropriate solvent without a glycol component because they do not use immunoassay methods for drug concentration measurements. To preclude the glycol component of Meucci would be contrary to the immunoassay method of Meucci for measuring drug concentration. Meucci uses an optional acid to precipitate and denature the interfering proteins.

In the presently claimed invention, an optional antioxidant, which can be an acid, is included. As further discussed above, both zinc sulfate concentration, and appropriate solvent, are critical to the present invention because they provide conditions to make it possible to recover at least 97% of the drug through a simplified and effective deproteinizing step from body fluids, allowing the drug detection in body fluids down to at least 0.3 µg/ml, using simpler detection methods, such as colorimetric assays.

As for the sample preparation methods of the presently claimed invention, the applicants again submit that Meucci uses different components for different purposes than the instantly claimed invention.

A basic difference is that, after protein precipitation, Meucci (such as in claim 11) performs immunological detection, which requires a precipitation reagent containing glycol with the purposes described in the above. Moreover, the presently claimed method provides detection of drug concentration in body fluid down to at least 0.3μ g/ml.

Finally, the presently claimed invention provides, contrary to Lam, precipitation and stripping in a single step, as described at page 14, lines 1-7 of the specification. The presently claimed method can also be used on smaller samples and with more analytes, which is not provided by the combined teachings of Meucci and Lam.

In view of the above, the claims, as amended, are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:plb
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100